CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER
NDA 20-665/S-016
NDA 21-283/S-001

ENVIRONMENTAL ASSESSMENT/FONSI

ENVIRONMENTAL ASSESSMENT

AND

FINDING OF NO SIGNIFICANT IMPACT

FOR

NDA 20-665/S-016

Diovan®

(Valsartan Capsules; 80 and 160 mg)

Division of Cardio-Renal Drug Products (HFD-110)
Center for Drug Evaluation and Research

FINDING OF NO SIGNIFICANT IMPACT

NDA 20-665/S-016

Diovan®

(Valsartan Capsules; 80 and 160 mg)

The National Environmental Policy Act of 1969 (NEPA) requires all Federal agencies to assess the environmental impact of their actions. FDA is required under NEPA to consider the environmental impact of approving certain drug product applications as an integral part of its regulatory process.

The Food and Drug Administration, Center for Drug Evaluation and Research has carefully considered the potential environmental impact of this action and has concluded that this action will not have a significant effect on the quality of the human environment and that an environmental impact statement is not required.

In support of their supplemental new drug application for Diovan® (Valsartan Capsules), 80 and 160 mg, Novartis Pharmaceutical Corporation has prepared an environmental assessment (attached) in accordance with 21 CFR Part 25 which evaluates the potential environmental impacts of the use and disposal from use of the product.

Valsartan is a chemically synthesized drug which is currently indicated for the treatment of hypertension, and may be used alone or in combination with other antihypertensive agents. This submissions supports the use of Diovan for the treatment of congestive heart failure.

Investigation of environmental depletion mechanisms demonstrated that valsartan would be hydrolytically stable over the environmental pH range at 50°C, and would not be expected to biodegrade under either aerobic or anaerobic conditions during waste water treatment. Based on these factors and the calculation of EIC, the evaluation of the environmental effects of the pharmacologically active parent compound, valsartan, was limited to the aquatic environment.

The results of toxicity studies indicate that the compound will have no effect on organisms at the expected environmental concentrations. Therefore, no adverse environmental effects are expected to result from this action.

Diovan® (valsartan capsules), 80 and 160 mg will be used primarily by patients in their homes and in hospitals and clinics, through physician prescription. Disposal of prescribed drug product will be through use, with returned product disposed through high temperature incineration at licensed disposal facilities. U.S. hospitals, pharmacies, or clinics will dispose of empty or partially empty packages in accordance with their internal waste handling procedures. In the home, disposal will be through community solid waste management systems, which may include landfills, incineration and recycling, although minimal quantities of the unused drug could be disposed of in

the sewer system.

The Center for Drug Evaluation and Research has concluded that the product can be used and disposed of without any expected adverse environmental effects. Adverse effects are not anticipated upon endangered or threatened species or upon property listed in or eligible for listing in the National Register of Historic Places.

PREPARED BY
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Attachments: Environmental Assessment
Appended Electronic Signature Page

NOVARTIS

Novartis Pharmaceuticals Corporation
East Hanover, New Jersey

DRA CMC Documentation

Diovan® (valsartan)
Congestive Heart Failure Indication

Environmental Assessment

Author(s):	Joyce Ann Sinno, Ph.D.
Document type:	Environmental Assessment
Document status:	Final
Release date:	25-Jun-01
Number of pages:	13

1. Date

Original submission for Congestive Heart Failure (CHF): document dated 17-Apr-01. This document was subsquently withdrawn from the SNDA on 7-May-01.

Amendment (current submission): document dated 25-Jun-01

Reference is also made to Environmental Assessments submitted to related Diovan NDAs:
Diovan Capsules, Original NDA #20-665: document dated 20-Nov-95
Amendment, submitted 30-May-96
Amendment, submitted 22-Oct-96.
Diovan HCT Tablets , Original NDA #20-818: document dated 18-Mar-97.
Diovan Tablets, Original NDA #21-283: document dated 03-Aug-00.

All environmental fate and effects study reports previously submitted to the Diovan Capsule NDA 20-665 and reviewed by the Agency have not been included in this Assessment.

2. Name of Applicant/Petitioner

Novartis Pharmaceuticals Corporation

3. Address

59 Route 10
East Hanover, NJ 07936-1080

4. Description of proposed action

4.1. Requested Approval

Novartis Pharmaceuticals Corporation has filed a supplement to NDA 20-665 (S-016) pursuant to section 505b of the FD&C Act for the use of Diovan® (valsartan) in the treatment of congestive heart failure. An Environmental Assessment (EA) has been submitted pursuant to 21 CFR part 25.

4.2. Need for Action

Diovan is currently indicated for the treatment of hypertension, and may be used alone or in combination with other antihypertensive agents. This submission supports the use of Diovan for the treatment of congestive heart failure.

4.3. Locations of Use

Patients with hypertension or congestive heart failure will use Diovan drug products in their homes, in clinics and in hospitals.

4.4. Disposal Sites

Hospitals, pharmacies and clinics will dispose of empty or partially empty packages of drug product according to their internal established procedures. In the home, empty or partially empty containers will typically be disposed of by the community's solid waste management system, which may include landfills, incineration and recycling. Minimal quantities of the unused drug may potentially be disposed of directly into the sewer system.

Rejected materials from the Novartis facility at Suffern, NY are incinerated at the American Ref-Fuel (Hempstead) Facility, 600 Avenue C, Westbury, NY 11590.

5. Identification of substances that are the subject of the proposed action

5.1. Nomenclature

5.1.1. Established Name (U.S. Adopted Name – USAN)

Valsartan

5.1.2. Brand/Proprietary Name/Tradename

Diovan®

5.1.3. Chemical Names

Chemical Abstracts Index Name

L-Valine, *N*-(1-oxopentyl)-*N*-[[2'-(1*H*-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-

Systematic Chemical Name (IUPAC)

(S)-2-{*N*-(1-oxopentyl)-*N*-[[2'-(1H-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl]methyl]-amino}-3-methyl-butyric acid

5.1.4. Other names

CGP 48933 (research code)

5.2. Chemical Abstracts Service (CAS) Registration Number

137862-53-4

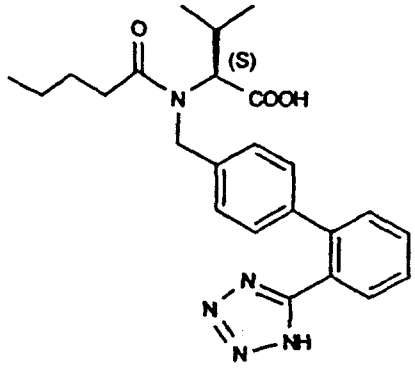
5.3. Molecular Formula

$C_{24}H_{29}N_5O_3$

5.4. Molecular Weight

435.5

5.5. Structural (graphic) Formula



6. Environmental issues

6.1. Physical and chemical characterization

Physical and chemical properties and constants were determined for Diovan drug substance, valsartan, and initially reported in Diovan 80 and 160 mg Capsules, Original NDA #20-665 (submitted 28-Dec-95; approved 23-Dec-96). For the convenience of the reviewer, this information is presented again in the present Environmental Assessment.

Studies to determine dissociation constant, water solubility, the octanol/water partition coefficient, vapor pressure, and ultraviolet-visible absorption were conducted under FDA Good Laboratory Practice (GLP) protocols utilizing Technical Assistance Documents (TAD) from the US FDA *Environmental Assessment Technical Assistance Handbook*[1].

The values obtained for each of these studies are presented in the Data Summary Table (Table 1) located at the end of this report. The full study reports were initially submitted in Diovan Capsules, Original NDA #20-665 and again in Diovan Tablets, Original NDA #21-283. Since these study reports were previously reviewed and approved by the Agency, they are **not provided** in the present Environmental Assessment.

6.1.1. Dissociation constant (TAD Section 3.04)

The pK_a value of valsartan was determined in CO_2-free reagent water at 25°C. Under the conditions of this study, two pKa's were determined: 3.76 (carboxylic group) and 5.60 (tetrazole group). Since valsartan has been shown to dissociate, water solubility and octanol/water partition coefficient were determined at pH 5, 7 and 9.

The mean pKa's are reported in the Data Summary Table (Table 1).

6.1.2. Water solubility (TAD Section 3.01)

The mean solubility of valsartan was determined at 25°C in aqueous buffers at pH 5, 7 and 9. Valsartan was determined to have a pH-dependent solubility in water. Due to the solubility

and strong acidity of valsartan, the pH 7 and 9 buffer capacities were exceeded and the final values for pH were between 5.2 and 5.6. The mean solubility (N = 6) at each pH is reported as follows:

	pH 5	pH 7	pH 9
Mean solubility (mg/L)	2990	8210	1470
Standard deviation	196	430	186
Final pH range	5.2 - 5.6	5.2 - 5.6	5.2 - 5.6

The mean solubility of valsartan (mg/L) at each pH level is reported in the Data Summary Table (Table 1).

6.1.3. n-Octanol/water partition coefficient (TAD Section 3.02)

The n-octanol/water partition coefficient (K_{ow}) for valsartan was determined by the shake flask method using ^{14}C-labeled material. Partitioning testing was conducted in triplicate at pH 5, 7 and 9 aqueous buffers at 25 ± 2 °C using nominal concentrations of 0.001 and 0.0001 M in n-octanol-saturated buffer at each pH. The following mean values were observed:

pH	Initial Buffer Concentration moles/L	mean K_{ow}	Log P
5	9.85×10^{-4}	32.2	1.51
	1.07×10^{-4}	31.8	1.50
7	1.04×10^{-3}	6.78×10^{-2}	-1.17
	1.09×10^{-4}	9.83×10^{-2}	-1.01
9	1.04×10^{-3}	1.43×10^{-2}	-1.84
	1.10×10^{-4}	1.82×10^{-2}	-1.74

Based upon the mean K_{ow} and the log P [log K_{ow}] values obtained in this study, valsartan is not expected to significantly bioconcentrate in living organisms or to sorb onto organic particles. Further, since the log K_{ow} was less than 3 at all pH levels tested, no further sorption/desorption properties (log K_{oc}) were considered.

The mean log n-octanol/water partition coefficient (log P) of valsartan at each pH level is reported in the Data Summary Table (Table 1).

6.1.4. Vapor pressure (TAD 3.03)

The vapor pressure of valsartan was determined in triplicate by the gas saturation method at 25°C using nitrogen flow rates of 5, 10 and 20 ml/min over a period of 16 days. No valsartan was detected in the sorbent martial at any of the flow rates. The detection limit of the instrumentation was therefore used to determine the vapor pressure of valsartan. The equilibrium vapor pressure of valsartan at 25°C was determined to be less than 1.33×10^{-5} Pa

at the nitrogen flow rate of 20 ml/min, or less than 1.0×10^{-5} torr. This corresponds to a Henry's Law Constant (H) less than 1.30×10^{-8}.

Based upon the Henry's Law Constant, valsartan would not be expected to be released into the air or have a significant vapor pressure.

The Henry's Law Constant for valsartan is reported in the Data Summary Table (Table 1).

6.1.5. Ultraviolet-visible absorption spectrum (TAD 3.05)

Ultraviolet/visible spectra were obtained for valsartan at pH 5, 7 and 9. Valsartan in pH 5.00 buffer exhibited no absorption peaks. Absorption spectra in pH 7.01 buffer consisted of one major peak at 209 nm and two shoulders at 250 nm and 229 nm. Absorption spectra of valsartan in buffer at pH 8.96 consisted of one major peak at 207 nm and two shoulders at 229 nm and 251 nm.

The absorption spectra for valsartan are reported in the Data Summary Table (Table 1).

6.2. Environmental depletion mechanisms

Environmental depletion mechanisms were investigated for valsartan. Studies to determine hydrolysis and aerobic biodegradation were conducted under FDA Good Laboratory Practice (GLP) protocols utilizing Technical Assistance Documents (TAD) from the US FDA *Environmental Assessment Technical Assistance Handbook*[2] as a guide.

6.2.1. Aqueous hydrolysis rate constant and half-life (TAD Section 3.09)

The first environmental depletion mechanism investigated was hydrolysis. Preliminary testing of ^{14}C-labeled valsartan was conducted over a 5-day period as per TAD, Section 3.09. Under the test conditions employed (50°C and all solutions removed from light), valsartan was determined to be hydrolytically stable at pH 5, 7 and 9 at 50°C. Based on these results, a half-life equal to or greater than one year at 25 °C was estimated using the criteria established in TAD, Section 3.09.

The hydrolysis half-life is reported in the Data Summary Table (Table 1).

6.2.2. Aerobic biodegradation (modified TAD Section 3.11)

Since valsartan was considered to be hydrolytically stable, aerobic biodegradation was investigated as a potential depletion mechanism. The aerobic biodegradation of valsartan was determined in a batch-activated sludge (BAS) system. The method followed FDA TAD 3.11, with some modifications. Labeled test article was added to sludge obtained from a municipal wastewater treatment plant and aerobically incubated in the dark for 28 days at 22 $\pm$ 2 °C. Since only slight transformation of the test article occurred with essentially no mineralization, the test was continued for another 10 days under these conditions. After 38 days, aeration to the system was discontinued, and the test system was incubated anaerobically for one month. At the end of one month, the systems were again sampled and assayed. Again, no significant degradation of the test article or mineralization occurred during the anaerobic portion of the

study. The BAS test system was validated by the reference test article, [^{14}C]sodium benzoate, which resulted in approximately 80% evolved $^{14}CO_2$ over the 28-day study.

Aerobic biodegradation in the wastewater treatment process may not be considered an important environmental depletion mechanism for valsartan.

The results of the biodegradation study are reported in the Data Summary Table (Table 1).

6.3. Environmental concentration

6.3.1. Expected Introduction Concentration (EIC)

As described in the July 1998 *Guidance for Industry: Environmental Assessment of Human Drugs and Biologics Applications*[3], the Expected Introduction Concentration (EIC) of an active moiety into the aquatic environment may be calculated as follows:

EIC-Aquatic (ppb) = A x B x C x D, where:

A = kg / yr produced for direct use (as active moiety)
B = 1 / 1.214 x 10^{11} liters per day entering POTWs [1996 Needs Survey, Report to Congress]
C = 1 year / 365 days per year
D = 10^9 µg/kg (conversion factor)

The EIC of valsartan has been calculated for the peak production year using estimates of Diovan drug substance requirements for both the hypertensive and congestive heart failure indications (Confidential Appendix 11.2.1.). The calculated EIC is provided in Confidential Appendix 11.2.2.

Novartis Pharmaceuticals is confident that the actual EIC will not exceed these estimates by an order of magnitude.

6.4. Summary

6.4.1. Aquatic environment

Valsartan is pharmacologically active and is rapidly absorbed following oral administration. Since valsartan exists as a di-anion with a double negative charge at physiological pH, the compound is very hydrophilic, and may therefore be a poor substrate for metabolizing enzymes.

A study using radiolabeled valsartan solution showed that valsartan is metabolized to a small extent only. The only notable metabolite detectable in the plasma is the valeryl-4-hydroxy valsartan (M1), an oxidized form of valsartan. Since this metabolite has not demonstrated any pharmacological activity *in vitro*, the biotransformation of valsartan to M1 can be described as an additional minor elimination process.

Valsartan is predominantly excreted as unchanged drug through feces, most likely via biliary elimination. Excretion is 99% complete within 7 days. Renal excretion, which accounts for 5

to 13% of the oral dose, is essentially complete within 48 hours. The bulk of the dose (83%) is excreted with the feces within 4 days. About 81% of the dose is excreted as unchanged valsartan, 9% as the valeryl-4-hydroxy metabolite (M1) and about 6% as other unidentified compounds in the feces and urine.

Studies were conducted to accurately determine the water solubility and partition coefficient of valsartan at pH 5.0, 7.0 and 9.0 at 25 ± 2 °C. The results of the water solubility study indicate that valsartan would be relatively soluble in water over the environmental pH range. The n-octanol/water partition coefficient, which indicates the tendency of a non-ionized organic chemical to accumulate in fatty tissue and to sorb onto soil particles or other organic matter, suggests that valsartan would not be expected to sorb significantly to the organic material in soil or sediment, and would not be expected to bioconcentrate substantially in aquatic organisms. (Chemicals with a log P less than 1 are not expected to significantly bioconcentrate or sorb, whereas chemicals with a log P greater than or equal to 4 may be expected to bioconcentrate or sorb significantly.) The calculated results presented in Tables 2 and 3 for the bioconcentration factor (BCF) and the soil adsorption coefficient (K_{oc}) further support the conclusion that valsartan would be expected to remain mobile in the aquatic compartment, and would not be expected to bioconcentrate or bioaccumulate.

Results of the ultraviolet/visible spectra scan indicated absorbance below 290 nm in aqueous buffer solutions over the environmental pH range. Direct photodegradation would not be considered a potential mechanism of depletion.

Investigations of environmental depletion mechanisms demonstrated that valsartan would be hydrolytically stable over the environmental pH range at 50°C, and would not be expected to biodegrade under either aerobic or anaerobic conditions during waste water treatment.

Five-year production estimates for Diovan drug products indicate that during the peak year, the EIC of valsartan at the point of entry into the aquatic environment will be greater than 1 ppb. Novartis Pharmaceuticals is confident that the actual EIC will not exceed these estimates by an order of magnitude.

Based upon these factors, the evaluation of the environmental effects of the pharmacologically active parent compound, valsartan, was limited to the aquatic environment.

6.5. Environmental effects of released substances

The environmental effects of valsartan was evaluated in the aquatic environment following the "Tiered Approach to Fate and Effects Testing" (Figure 1, July 1998 EA *Guidance for Industry*[3]). With no rapid, complete environmental depletion mechanism identified, microbial inhibition was evaluated in accordance with Technical Assistance Document (TAD), Section 4.02[4]. Additionally, since the Log K_{ow} was less than 3.5, acute toxicity testing was conducted in *Daphnia magna* utilizing TAD 4.08 from the US FDA *Environmental Assessment Technical Assistance Handbook*[4]. Both studies were conducted under FDA Good Laboratory Practices (GLPs).

6.5.1. Microbial inhibition test

The agar plate dilution method was used to evaluate the toxicity of valsartan to pure cultures of molds, ascomycetes, free-living nitrogen-fixing and soil bacteria, and blue-green algae. The minimum inhibitory concentrations (MIC) established for valsartan for these five representative cultures are:

Species	MIC (mg/L)
Aspergillus niger	> 1000
Trichoderma viride	> 1000
Clostridium perfringens	> 1000
Bacillus subtilis	1000
Nostoc sp.	200

Results indicate valsartan is non-inhibitory to microorganisms which may be found in activated sludge.

Results are reported in the Data Summary Table (Table 1).

6.5.2. Acute toxicity in *Daphnia magna* (TAD 4.08)

With no depletion mechanism identified and with a Log K_{ow} < 3.5, a forty-eight hour acute toxicity study was conducted on one suitable test organism (an aquatic invertebrate) to further evaluate the ecotoxicity of valsartan, as described in the "Tiered Approach to Fate and Effects Testing".

Acute toxicity testing was conducted in *Daphnia magna* under static conditions following the protocol described in *FDA Environmental Assessment Technical Assistance Handbook*, Document 4.08. Based on the results of this study, the 48-hour median effect concentration (EC_{50}) for valsartan was estimated to be 580 mg/L, and the No-Observed-Effect-Concentration (NOEC) was determined to be 280 mg/L.

Results are reported in the Data Summary Table (Table 1).

6.5.3. Assessment factor

As described in the July 1998 *Guidance for Industry: Environmental Assessment of Human Drugs and Biologics Applications*[3], an Assessment Factor is a toxicity ratio which provides a consistent regulatory basis for determining if and when additional ecotoxicity testing should be performed, using a tiered approach. The Assessment Factor may be calculated by dividing an appropriate acute toxicity test endpoint by the MEEC (Maximum Expected Environmental Concentration). An Assessment Factor greater than 1000 would not require additional ecotoxicity testing.

In the case of valsartan, by applying the 48-hour EC_{50} from the *Daphnia magna* study and the calculation of the EIC (Confidential Appendix 11.2.2.), an Assessment Factor of [>>>10,000] is obtained. (Calculation of the Assessment Factor is provided in Confidential Appendix 11.2.3.) Thus, no additional ecotoxicity testing is required for valsartan. Since the

Assessment Factor calculated for valsartan is significantly more than one order of magnitude greater than that reported in the Guidance Document, the results suggest valsartan would be nontoxic in the aquatic environment.

7. Mitigation measures

Based upon the information and data presented in this environmental assessment, Novartis Pharmaceuticals has concluded that no potential adverse environmental impacts are foreseen with the packaging, distribution, use or disposal of Diovan drug products within the United States. No mitigation measures are considered necessary.

8. Alternatives to the proposed action

No alternatives to the proposed action are suggested, as no potential adverse environmental impacts have been identified for the packaging, distribution, use or disposal of Diovan drug products. The use of Diovan drug products will directly benefit patients suffering from hypertension.

It is our conclusion that approval of this Application is therefore preferable to non-approval.

9. List of preparers

Curriculum vitae, documenting the qualifications and credentials of the contributors to this environmental assessment, are provided in Non-confidential Appendix 11.1.1.

10. References

1. US FDA, March 1987. Environmental Assessment Technical Assistance Handbook, TAD Sections 3.01, 3.02, 3.03, 3.04, and 3.05.

2. US FDA, March 1987. Environmental Assessment Technical Assistance Handbook, Sections 3.09 and 3.11 (modified).

3. US Food and Drug Administration, Center for Drug Evaluation and Research (CDER) and Center for Biologics Evaluation and Research (CBER), July 1998. Guidance for Industry: Environmental Assessment of Human Drugs and Biologics Applications. CMC 6, Revision 1.

4. US FDA, March 1987. Environmental Assessment Technical Assistance Handbook, Sections 4.02 and 4.08.

11. Appendices

11.1. Non-confidential appendix

11.1.1. Curriculum vitae of contributors

11.2. Confidential appendices

11.2.1. Production estimates of Diovan drug substance requirements, date 15-Mar-01.

11.2.2. Expected Introduction Concentration (EIC) of valsartan based upon production estimates, dated 15-Mar-01.

11.2.3. Calculation of Assessment Factor, dated 15-Mar-01.

Table 1. Data Summary Table

DATA SUMMARY TABLE

PHYSICAL / CHEMICAL CHARACTERIZATION	
Water Solubility – mean (mg/L)	2990 @ pH 5 8210 @ pH 7 1470 @ pH 9
Dissociation Constants (mean pKa's)	3.76 (carboxylic group) and 5.60 (tetrazole group)
Log n-Octanol/Water Partition Coefficient (Log K_{ow})	1.51 @ pH 5 in 9.85 x 10^{-4} moles/L buffer 1.50 @ pH 5 in 1.07 x 10^{-4} moles/L buffer -1.17 @ pH 7 in 1.04 x 10^{-3} moles/L buffer -1.01 @ pH 7 in 1.09 x 10^{-4} moles/L buffer -1.84 @ pH 9 in 1.04 x 10^{-3} moles/L buffer -1.74 @ pH 9 in 1.10 x 10^{-4} moles/L buffer
Henry's Law Constant (H)	< 1.30 x 10^{-8}
Ultraviolet-visible absorption spectrum	No absorption peaks @ pH 5. One main peak at 209 nm @ pH 7. One main peak at 207 nm @ pH 9.
DEPLETION MECHANISMS	
Hydrolysis	$t_{1/2} \geq$ 1 year at 25 °C
Aerobic Biodegradation	0.02 % ^{14}C evolved over 28-day aerobic study
Metabolism	Valsartan is predominantly excreted unchanged through feces, most likely via biliary elimination. Excretion is 99% complete within 7 days. Renal excretion, which accounts for 5 to 13% of the oral dose, is essentially complete within 48 hours. The bulk of the dose (83%) is excreted with the feces within 4 days. About 81% of the dose is excreted as unchanged valsartan, 9% as the valeryl-4-hydroxy metabolite (M1) and about 6% as other unidentified compounds in the feces and urine.
ENVIRONMENTAL EFFECTS	
Microbial Inhibition	**Species** — **MIC (mg/L)** *Aspergillus niger* — > 1000 *Trichoderma viride* — > 1000 *Clostridium perfringens* — > 1000 *Bacillus subtilis* — 1000 *Nostoc* sp. — 200
Acute Toxicity in *Daphnia magna*	EC_{50} = 580 mg/L NOEC = 280 mg/L

Calculated environmental fate results

Table 2. Calculated results for the bioconcentration factor (BCF) and the soil adsorption coefficient (K_{oc}) for valsartan based upon experimentally determined mean water solubility

	pH 5	pH 7	pH 9
Water solubility (mg/L)	2990	8210	1470
BCF [a]	6.77	3.83	2.76
K_{oc} [b]	53.5	30.7	22.3

[a] Log (BCF) = 2.791 – 0.564 Log (S), where S = water solubility in mg/L.
[b] Log (K_{oc}) = 3.64 – 0.55 Log (S), where S = water solubility in mg/L.

Table 3. Calculated results for the bioconcentration factor (BCF) and the soil adsorption coefficient (K_{oc}) for valsartan based upon experimentally determined partition coefficient (log K_{ow})

	Range	
	Low	High
BCF [a]	0.0135X	6.32X
K_{oc} [b]	2.32	160

The highest (-1.86) and lowest (1.52) log K_{ow} values were used to calculate the BCF and K_{ow}.
[a] Log (BCF) = (0.79 x log K_{ow}) – 0.40 (Kenaga and Goring, 1980)
[b] Log (K_{oc}) = (0.544 x log K_{ow}) + 1.377 (Kenaga and Goring, 1980)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

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7/19/01 12:46:02 PM

Nancy Sager
7/19/01 12:50:38 PM

Yuan-Yuan Chiu
7/20/01 06:33:36 PM
concur

ENVIRONMENTAL ASSESSMENT

AND

FINDING OF NO SIGNIFICANT IMPACT

FOR

NDA 21-283/S-001

Diovan®

(Valsartan Tablets)

Division of Cardio-Renal Drug Products (HFD-110)
Center for Drug Evaluation and Research

FINDING OF NO SIGNIFICANT IMPACT

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The Food and Drug Administration, Center for Drug Evaluation and Research has carefully considered the potential environmental impact of this action and has concluded that this action will not have a significant effect on the quality of the human environment and that an environmental impact statement is not required.

In support of their supplemental new drug application for Diovan® (Valsartan Tablets), Novartis Pharmaceutical Corporation has prepared an environmental assessment (attached) in accordance with 21 CFR Part 25 which evaluates the potential environmental impacts of the use and disposal from use of the product.

Valsartan is a chemically synthesized drug currently indicated for the treatment of hypertension, and may be used alone or in combination with other antihypertensive agents This submission supports the use of Diovan for the treatment of congestive heart failure.

Investigation of environmental depletion mechanisms demonstrated that valsartan would be hydrolytically stable over the environmental pH range at 50°C, and would not be expected to biodegrade under either aerobic or anaerobic conditions during waste water treatment. Based on these factors and the calculation of EIC, the evaluation of the environmental effects of the pharmacologically active parent compound, valsartan, was limited to the aquatic environment.

The results of toxicity studies indicate that the compound will have no effect on organisms at the expected environmental concentrations. Therefore, no adverse environmental effects are expected to result from this action.

Diovan® (valsartan tablets) will be used primarily by patients in their homes and in hospitals and clinics, through physician prescription. Disposal of prescribed drug product will be through use, with returned product disposed through high temperature incineration at licensed disposal facilities. U.S. hospitals, pharmacies, or clinics will dispose of empty or partially empty packages in accordance with their internal waste handling procedures. In the home, disposal will be through community solid waste management systems, which may include landfills, incineration and recycling, although minimal quantities of the unused drug could be disposed of in the sewer

system.

The Center for Drug Evaluation and Research has concluded that the product can be used and disposed of without any expected adverse environmental effects. Adverse effects are not anticipated upon endangered or threatened species or upon property listed in or eligible for listing in the National Register of Historic Places.

PREPARED BY
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CONCURRED BY
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Environmental Officer, Center for Drug Evaluation and Research

CONCURRED BY
Yuan-yuan Chiu, Ph.D.
Director, Office of New Drug Chemistry
Center for Drug Evaluation and Research

Attachments: Environmental Assessment
Appended Electronic Signature Page

NOVARTIS

Novartis Pharmaceuticals Corporation
East Hanover, New Jersey

DRA CMC Documentation

Diovan® Tablets (valsartan)
40 mg

Environmental Assessment

Author(s):	Joyce Ann Sinno, Ph.D.
Document type:	Environmental Assessment
Document status:	Final
Release date:	5-Jul-2001
Number of pages:	13

1. Date

Amendment (current submission): document dated 5-Jul-00. This document is identical to the Amendment for Congestive Heart Failure (CHF), dated 25-Jun-01 which was submitted to the Diovan Capsule NDA. The CHF indication is filed to the Diovan Capsule NDA. All CMC information for Diovan Tablets is filed to the Diovan Tablet NDA.

Reference is also made to Environmental Assessments submitted to related Diovan NDAs:

Diovan Capsules, Original NDA #20-665: document dated 20-Nov-95
Amendment, submitted 30-May-96
Amendment, submitted 22-Oct-96.
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Diovan HCT Tablets , Original NDA #20-818: document dated 18-Mar-97.

Diovan Tablets, Original NDA #21-283: document dated 03-Aug-00.

All environmental fate and effects study reports previously submitted to the Diovan Capsule NDA 20-665 and reviewed by the Agency have not been included in this Assessment.

2. Name of Applicant/Petitioner

Novartis Pharmaceuticals Corporation

3. Address

59 Route 10

East Hanover, NJ 07936-1080

4. Description of proposed action

4.1. Requested Approval

Novartis Pharmaceuticals Corporation has filed a supplement to NDA 21-283 (S-001) pursuant to section 505b of the FD&C Act for Diovan® (valsartan) Tablets 40 mg. An Environmental Assessment (EA) has been submitted pursuant to 21 CFR part 25.

4.2. Need for Action

Diovan is currently indicated for the treatment of hypertension, and may be used alone or in combination with other antihypertensive agents. This submission supports the use of Diovan for the treatment of congestive heart failure.

4.3. Locations of Use

Patients with hypertension or congestive heart failure will use Diovan drug products in their homes, in clinics and in hospitals.

4.4. Disposal Sites

Hospitals, pharmacies and clinics will dispose of empty or partially empty packages of drug product according to their internal established procedures. In the home, empty or partially empty containers will typically be disposed of by the community's solid waste management system, which may include landfills, incineration and recycling. Minimal quantities of the unused drug may potentially be disposed of directly into the sewer system.

Rejected materials from the Novartis facility at Suffern, NY are incinerated at the American Ref-Fuel (Hempstead) Facility, 600 Avenue C, Westbury, NY 11590.

5. Identification of substances that are the subject of the proposed action

5.1. Nomenclature

5.1.1. Established Name (U.S. Adopted Name – USAN)

Valsartan

5.1.2. Brand/Proprietary Name/Tradename

Diovan®

5.1.3. Chemical Names

Chemical Abstracts Index Name

L-Valine, *N*-(1-oxopentyl)-*N*-[[2'-(1*H*-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-

Systematic Chemical Name (IUPAC)

(S)-2-{*N*-(1-oxopentyl)-*N*-[[2'-(1H-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl]methyl]-amino}-3-*methyl-butyric acid*

5.1.4. Other names

CGP 48933 (research code)

5.2. Chemical Abstracts Service (CAS) Registration Number

137862-53-4

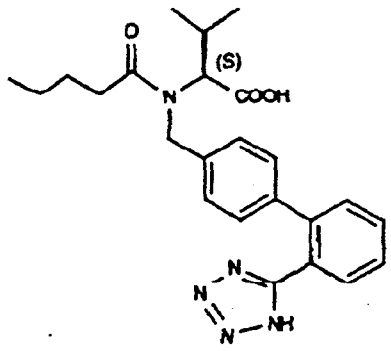
5.3. Molecular Formula

$C_{24}H_{29}N_5O_3$

5.4. Molecular Weight

435.5

5.5. Structural (graphic) Formula



6. Environmental Issues

6.1. Physical and chemical characterization

Physical and chemical properties and constants were determined for Diovan drug substance, valsartan, and initially reported in Diovan 80 and 160 mg Capsules, Original NDA #20-665 (submitted 28-Dec-95; approved 23-Dec-96). For the convenience of the reviewer, this information is presented again in the present Environmental Assessment.

Studies to determine dissociation constant, water solubility, the octanol/water partition coefficient, vapor pressure, and ultraviolet-visible absorption were conducted under FDA Good Laboratory Practice (GLP) protocols utilizing Technical Assistance Documents (TAD) from the US FDA *Environmental Assessment Technical Assistance Handbook*[1].

The values obtained for each of these studies are presented in the Data Summary Table (Table 1) located at the end of this report. The full study reports were initially submitted in Diovan Capsules, Original NDA #20-665 and again in Diovan Tablets, Original NDA #21-283. Since these study reports were previously reviewed and approved by the Agency, they are **not provided** in the present Environmental Assessment.

6.1.1. Dissociation constant (TAD Section 3.04)

The pK_a value of valsartan was determined in CO_2-free reagent water at 25°C. Under the conditions of this study, two pKa's were determined: 3.76 (carboxylic group) and 5.60 *(tetrazole group). Since valsartan has been shown to dissociate,* water solubility and octanol/water partition coefficient were determined at pH 5, 7 and 9.

The mean pKa's are reported in the Data Summary Table (Table 1).

6.1.2. Water solubility (TAD Section 3.01)

The mean solubility of valsartan was determined at 25°C in aqueous buffers at pH 5, 7 and 9. Valsartan was determined to have a pH-dependent solubility in water. Due to the solubility and strong acidity of valsartan, the pH 7 and 9 buffer capacities were exceeded and the final values for pH were between 5.2 and 5.6. The mean solubility (N = 6) at each pH is reported as follows:

	pH 5	pH 7	pH 9
Mean solubility (mg/L)	2990	8210	1470
Standard deviation	196	430	186
Final pH range	5.2 - 5.6	5.2 - 5.6	5.2 - 5.6

The mean solubility of valsartan (mg/L) at each pH level is reported in the Data Summary Table (Table 1).

6.1.3. n-Octanol/water partition coefficient (TAD Section 3.02)

The n-octanol/water partition coefficient (K_{ow}) for valsartan was determined by the shake flask method using ^{14}C-labeled material. Partitioning testing was conducted in triplicate at pH 5, 7 and 9 aqueous buffers at 25 ± 2 °C using nominal concentrations of 0.001 and 0.0001 M in n-octanol-saturated buffer at each pH. The following mean values were observed:

pH	Initial Buffer Concentration moles/L	mean K_{ow}	Log P
5	9.85×10^{-4}	32.2	1.51
	1.07×10^{-4}	31.8	1.50
7	1.04×10^{-3}	6.78×10^{-2}	-1.17
	1.09×10^{-4}	9.83×10^{-2}	-1.01
9	1.04×10^{-3}	1.43×10^{-2}	-1.84
	1.10×10^{-4}	1.82×10^{-2}	-1.74

Based upon the mean K_{ow} and the log P [log K_{ow}] values obtained in this study, valsartan is not expected to significantly bioconcentrate in living organisms or to sorb onto organic particles. Further, since the log K_{ow} was less than 3 at all pH levels tested, no further sorption/desorption properties (log K_{oc}) were considered.

The mean log n-octanol/water partition coefficient (log P) of valsartan at each pH level is reported in the Data Summary Table (Table 1).

6.1.4. Vapor pressure (TAD 3.03)

The vapor pressure of valsartan was determined in triplicate by the gas saturation method at 25°C using nitrogen flow rates of 5, 10 and 20 ml/min over a period of 16 days. No valsartan was detected in the sorbent martial at any of the flow rates. The detection limit of the instrumentation was therefore used to determine the vapor pressure of valsartan. The equilibrium vapor pressure of valsartan at 25°C was determined to be less than 1.33×10^{-3} Pa at the nitrogen flow rate of 20 ml/min, or less than 1.0×10^{-5} torr. This corresponds to a Henry's Law Constant (H) less than 1.30×10^{-6}.

Based upon the Henry's Law Constant, valsartan would not be expected to be released into the air or have a significant vapor pressure.

The Henry's Law Constant for valsartan is reported in the Data Summary Table (Table 1).

6.1.5. Ultraviolet-visible absorption spectrum (TAD 3.05)

Ultraviolet/visible spectra were obtained for valsartan at pH 5, 7 and 9. Valsartan in pH 5.00 buffer exhibited no absorption peaks. Absorption spectra in pH 7.01 buffer consisted of one major peak at 209 nm and two shoulders at 250 nm and 229 nm. Absorption spectra of valsartan in buffer at pH 8.96 consisted of one major peak at 207 nm and two shoulders at 229 nm and 251 nm.

The absorption spectra for valsartan are reported in the Data Summary Table (Table 1).

6.2. Environmental depletion mechanisms

Environmental depletion mechanisms were investigated for valsartan. Studies to determine hydrolysis and aerobic biodegradation were conducted under FDA Good Laboratory Practice (GLP) protocols utilizing Technical Assistance Documents (TAD) from the US FDA Environmental Assessment Technical Assistance Handbook[2] as a guide.

6.2.1. Aqueous hydrolysis rate constant and half-life (TAD Section 3.09)

The first environmental depletion mechanism investigated was hydrolysis. Preliminary testing of ^{14}C-labeled valsartan was conducted over a 5-day period as per TAD, Section 3.09. Under the test conditions employed (50°C and all solutions removed from light), valsartan was determined to be hydrolytically stable at pH 5, 7 and 9 at 50°C. Based on these results, a half-life equal to or greater than one year at 25 °C was estimated using the criteria established in TAD, Section 3.09.

The hydrolysis half-life is reported in the Data Summary Table (Table 1).

6.2.2. Aerobic biodegradation (modified TAD Section 3.11)

Since valsartan was considered to be hydrolytically stable, aerobic biodegradation was investigated as a potential depletion mechanism. The aerobic biodegradation of valsartan was determined in a batch-activated sludge (BAS) system. The method followed FDA TAD 3.11, with some modifications. Labeled test article was added to sludge obtained from a municipal wastewater treatment plant and aerobically incubated in the dark for 28 days at 22 ± 2 °C. Since only slight transformation of the test article occurred with essentially no mineralization, the test was continued for another 10 days under these conditions. After 38 days, aeration to the system was discontinued, and the test system was incubated anaerobically for one month. At the end of one month, the systems were again sampled and assayed. Again, no significant degradation of the test article or mineralization occurred during the anaerobic portion of the study. The BAS test system was validated by the reference test article, [^{14}C]sodium benzoate, which resulted in approximately 80% evolved $^{14}CO_2$ over the 28-day study.

Aerobic biodegradation in the wastewater treatment process may not be considered an important environmental depletion mechanism for valsartan.

The results of the biodegradation study are reported in the Data Summary Table (Table 1).

6.3. Environmental concentration

6.3.1. Expected Introduction Concentration (EIC)

As described in the July 1998 *Guidance for Industry: Environmental Assessment of Human Drugs and Biologics Applications*[3], the Expected Introduction Concentration (EIC) of an active moiety into the aquatic environment may be calculated as follows:

EIC-Aquatic (ppb) = A x B x C x D, where:

A = kg / yr produced for direct use (as active moiety)
B = 1 / 1.214 x 10^{11} liters per day entering POTWs [1996 Needs Survey, Report to Congress]
C = 1 year / 365 days per year
D = 10^9 µg/kg (conversion factor)

The EIC of valsartan has been calculated for the peak production year using estimates of Diovan drug substance requirements for both the hypertensive and congestive heart failure indications (Confidential Appendix 11.2.1.). The calculated EIC is provided in Confidential Appendix 11.2.2.

Novartis Pharmaceuticals is confident that the actual EIC will not exceed these estimates by an order of magnitude.

6.4. Summary

6.4.1. Aquatic environment

Valsartan is pharmacologically active and is rapidly absorbed following oral administration. Since valsartan exists as a di-anion with a double negative charge at physiological pH, the compound is very hydrophilic, and may therefore be a poor substrate for metabolizing enzymes.

A study using radiolabeled valsartan solution showed that valsartan is metabolized to a small extent only. The only notable metabolite detectable in the plasma is the valeryl-4-hydroxy valsartan (M1), an oxidized form of valsartan. Since this metabolite has not demonstrated any pharmacological activity *in vitro*, the biotransformation of valsartan to M1 can be described as an additional minor elimination process.

Valsartan is predominantly excreted as unchanged drug through feces, most likely via biliary elimination. Excretion is 99% complete within 7 days. Renal excretion, which accounts for 5 to 13% of the oral dose, is essentially complete within 48 hours. The bulk of the dose (83%) is excreted with the feces within 4 days. About 81% of the dose is excreted as unchanged valsartan, 9% as the valeryl-4-hydroxy metabolite (M1) and about 6% as other unidentified compounds in the feces and urine.

Studies were conducted to accurately determine the water solubility and partition coefficient of valsartan at pH 5.0, 7.0 and 9.0 at 25 $\pm$ 2 °C. The results of the water solubility study indicate that valsartan would be relatively soluble in water over the environmental pH range. The n-octanol/water partition coefficient, which indicates the tendency of a non-ionized organic chemical to accumulate in fatty tissue and to sorb onto soil particles or other organic matter, suggests that valsartan would not be expected to sorb significantly to the organic material in soil or sediment, and would not be expected to bioconcentrate substantially in aquatic organisms. (Chemicals with a log P less than 1 are not expected to significantly bioconcentrate or sorb, whereas chemicals with a log P greater than or equal to 4 may be expected to bioconcentrate or sorb significantly.) The calculated results presented in Tables 2 and 3 for the bioconcentration factor (BCF) and the soil adsorption coefficient (K_{oc}) further support the conclusion that valsartan would be expected to remain mobile in the aquatic compartment, and would not be expected to bioconcentrate or bioaccumulate.

Results of the ultraviolet/visible spectra scan indicated absorbance below 290 nm in aqueous buffer solutions over the environmental pH range. *Direct photodegradation would not be* considered a potential mechanism of depletion.

Investigations of environmental depletion mechanisms demonstrated that valsartan would be hydrolytically stable over the environmental pH range at 50°C, and would not be expected to biodegrade under either aerobic or anaerobic conditions during waste water treatment.

Five-year production estimates for Diovan drug products indicate that during the peak year, the EIC of valsartan at the point of entry into the aquatic environment will be greater than

1 ppb. Novartis Pharmaceuticals is confident that the actual EIC will not exceed these estimates by an order of magnitude.

Based upon these factors, the evaluation of the environmental effects of the pharmacologically active parent compound, valsartan, was limited to the aquatic environment.

6.5. Environmental effects of released substances

The environmental effects of valsartan was evaluated in the aquatic environment following the "Tiered Approach to Fate and Effects Testing" (Figure 1, July 1998 EA *Guidance for Industry*[3]). With no rapid, complete environmental depletion mechanism identified, microbial inhibition was evaluated in accordance with Technical Assistance Document (TAD), Section 4.02[4]. Additionally, since the Log K_{ow} was less than 3.5, acute toxicity testing was conducted in *Daphnia magna* utilizing TAD 4.08 from the US FDA *Environmental Assessment Technical Assistance Handbook*[4]. Both studies were conducted under FDA Good Laboratory Practices (GLPs).

6.5.1. Microbial inhibition test

The agar plate dilution method was used to evaluate the toxicity of valsartan to pure cultures of molds, ascomycetes, free-living nitrogen-fixing and soil bacteria, and blue-green algae. The minimum inhibitory concentrations (MIC) established for valsartan for these five representative cultures are:

Species	MIC (mg/L)
Aspergillus niger	> 1000
Trichoderma viride	> 1000
Clostridium perfringens	> 1000
Bacillus subtilis	1000
Nostoc sp.	200

Results indicate valsartan is non-inhibitory to microorganisms which may be found in activated sludge.

Results are reported in the Data Summary Table (Table 1).

6.5.2. Acute toxicity in *Daphnia magna* (TAD 4.08)

With no depletion mechanism identified and with a Log K_{ow} < 3.5, a forty-eight hour acute toxicity study was conducted on one suitable test organism (an aquatic invertebrate) to further evaluate the ecotoxicity of valsartan, as described in the "Tiered Approach to Fate and Effects Testing".

Acute toxicity testing was conducted in *Daphnia magna* under static conditions following the protocol described in *FDA Environmental Assessment Technical Assistance Handbook*, Document 4.08. Based on the results of this study, the 48-hour median effect concentration

(EC_{50}) for valsartan was estimated to be 580 mg/L, and the No-Observed-Effect-Concentration (NOEC) was determined to be 280 mg/L.

Results are reported in the Data Summary Table (Table 1).

6.5.3. Assessment factor

As described in the July 1998 *Guidance for Industry: Environmental Assessment of Human Drugs and Biologics Applications*[3], an Assessment Factor is a toxicity ratio which provides a consistent regulatory basis for determining if and when additional ecotoxicity testing should be performed, using a tiered approach. The Assessment Factor may be calculated by dividing an appropriate acute toxicity test endpoint by the *MEEC* (Maximum Expected Environmental Concentration). An Assessment Factor greater than 1000 would not require additional ecotoxicity testing.

In the case of valsartan, by applying the 48-hour EC_{50} from the *Daphnia magna* study and the calculation of the EIC (Confidential Appendix 11.2.2.), an Assessment Factor of [>>>10,000] is obtained. (Calculation of the Assessment Factor is provided in Confidential Appendix 11.2.3.) Thus, no additional ecotoxicity testing is required for valsartan. Since the Assessment Factor calculated for valsartan is significantly more than one order of magnitude greater than that reported in the Guidance Document, the results suggest valsartan would be nontoxic in the aquatic environment.

7. Mitigation measures

Based upon the information and data presented in this environmental assessment, Novartis Pharmaceuticals has concluded that no potential adverse environmental impacts are foreseen with the packaging, distribution, use or disposal of Diovan drug products within the United States. No mitigation measures are considered necessary.

8. Alternatives to the proposed action

No alternatives to the proposed action are suggested, as no potential adverse environmental impacts have been identified for the packaging, distribution, use or disposal of Diovan drug products. The use of Diovan drug products will directly benefit patients suffering from hypertension.

It is our conclusion that approval of this Application is therefore preferable to non-approval.

9. List of preparers

Curriculum vitae, documenting the qualifications and credentials of the contributors to this environmental assessment, are provided in Non-confidential Appendix 11.1.1.

10. References

1. US FDA, March 1987. Environmental Assessment Technical Assistance Handbook, TAD Sections 3.01, 3.02, 3.03, 3.04, and 3.05.

2. US FDA, March 1987. Environmental Assessment Technical Assistance Handbook, Sections 3.09 and 3.11 (modified).

3. US Food and Drug Administration, Center for Drug Evaluation and Research (CDER) and Center for Biologics Evaluation and Research (CBER), July 1998. Guidance for Industry: Environmental Assessment of Human Drugs and Biologics Applications. CMC 6, Revision 1.

4. US FDA, March 1987. Environmental Assessment Technical Assistance Handbook, Sections 4.02 and 4.08.

11. Appendices

11.1. Non-confidential appendix

11.1.1. Curriculum vitae of contributors

11.2. Confidential appendices

11.2.1. Production estimates of Diovan drug substance requirements, date 15-Mar-01.

11.2.2. Expected Introduction Concentration (EIC) of valsartan based upon production estimates, dated 15-Mar-01.

11.2.3. Calculation of Assessment Factor, dated 15-Mar-01.

Table 1. Data Summary Table

DATA SUMMARY TABLE		
PHYSICAL / CHEMICAL CHARACTERIZATION		
Water Solubility – mean (mg/L)	2990 @ pH 5 8210 @ pH 7 1470 @ pH 9	
Dissociation Constants (mean pKa's)	3.76 (carboxylic group) and 5.60 (tetrazole group)	
Log n-Octanol/Water Partition Coefficient (Log K_{ow})	1.51 @ pH 5 in 9.85 x 10^{-4} moles/L buffer 1.50 @ pH 5 in 1.07 x 10^{-4} moles/L buffer -1.17 @ pH 7 in 1.04 x 10^{-3} moles/L buffer -1.01 @ pH 7 in 1.09 x 10^{-4} moles/L buffer -1.84 @ pH 9 in 1.04 x 10^{-3} moles/L buffer -1.74 @ pH 9 in 1.10 x 10^{-4} moles/L buffer	
Henry's Law Constant (H)	< 1.30 x 10^{-8}	
Ultraviolet-visible absorption spectrum	No absorption peaks @ pH 5. One main peak at 209 nm @ pH 7. One main peak at 207 nm @ pH 9.	
DEPLETION MECHANISMS		
Hydrolysis	t ½ ≥ 1 year at 25 °C	
Aerobic Biodegradation	0.02 % ^{14}C evolved over 28-day aerobic study	
Metabolism	Valsartan is predominantly excreted unchanged through feces, most likely via biliary elimination. Excretion is 99% complete within 7 days. Renal excretion, which accounts for 5 to 13% of the oral dose, is essentially complete within 48 hours. The bulk of the dose (83%) is excreted with the feces within 4 days. About 81% of the dose is excreted as unchanged valsartan, 9% as the valeryl-4-hydroxy metabolite (M1) and about 6% as other unidentified compounds in the feces and urine.	
ENVIRONMENTAL EFFECTS		
Microbial Inhibition	**Species**	***MIC (mg/L)***
	Aspergillus niger	> 1000
	Trichoderma viride	> 1000
	Clostridium perfringens	> 1000
	Bacillus subtilis	1000
	Nostoc sp.	200
Acute Toxicity in *Daphnia magna*	EC_{50} = 580 mg/L NOEC = 280 mg/L	

Calculated environmental fate results

Table 2. Calculated results for the bioconcentration factor (BCF) and the soil adsorption coefficient (K_{oc}) for valsartan based upon experimentally determined mean water solubility

	pH 5	pH 7	pH 9
Water solubility (mg/L)	2990	8210	1470
BCF [a]	6.77	3.83	2.76
K_{oc} [b]	53.5	30.7	22.3

[a] Log (BCF) = 2.791 – 0.564 Log (S), where S = water solubility in mg/L.
[b] Log (K_{oc}) = 3.64 – 0.55 Log (S), where S = water solubility in mg/L.

Table 3. Calculated results for the bioconcentration factor (BCF) and the soil adsorption coefficient (K_{oc}) for valsartan based upon experimentally determined partition coefficient (log K_{ow})

	Range	
	Low	High
BCF [a]	0.0135X	6.32X
K_{oc} [b]	2.32	160

The highest (-1.86) and lowest (1.52) log K_{ow} values were used to calculate the BCF and K_{oc}.
[a] Log (BCF) = (0.79 x log K_{ow}) – 0.40 (Kenaga and Goring, 1980)
[b] Log (K_{oc}) = (0.544 x log K_{ow}) + 1.377 (Kenaga and Goring, 1980)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER
NDA 20-665/S-016
NDA 21-283/S-001

Pharmacology Review(s)

Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIO-RENAL DRUG PRODUCTS

DATE: 7/30/2001

FROM: Anthony G. Proakis, Ph.D., Pharmacology Reviewer, HFD-110

TO: Division Files

SUBJECT: Valsartan (DIOVAN™) Supplemental NDA #20665-SE1-016, # 21283-SE1-001.

At the 45-day NDA filing meeting on June 7, 2001, I stated that this supplemental application (CHF indication) for valsartan contains no new preclinical pharmacology/toxicology study reports requiring review. Likewise, the sponsor's proposed changes of the product labeling are limited to the clinical results and contain no changes from the previously approved summaries of the non-clinical studies. Therefore, a pharmacology/toxicology review for this NDA supplement is not necessary.

cc:
EFromm/HFD-110
CResnick/HFD-110